Different Hypotensive Responses to Intravenous Bovine and Human Thrombin Preparations in Swine

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Background: **Accidental intravenous introduction of commercial bovine thrombin (BT) during use of fibrin glue may result in profound hypotension. Commercial human thrombin (HT) is now available. This study compared the effects of intravenous BT versus HT in swine.**

Methods: **Swine received 30 U/kg BT, 60 U/kg BT, 30 U/kg HT, or 60 U/kg HT intravenously. Mean arterial pressure (MAP) and survival were monitored for 30 minutes. Thrombin purities and in vitro activities were examined.**

Results: **MAP nadir was lower ($p < 0.05$) after BT, 27.7 ± 3.3% (mean ± SEM) of pretreatment MAP, compared with 41.1 ± 3.7% after HT. Five of six animals died after 60 U/kg BT, whereas all others survived ($p < 0.05$). Histology suggested more severe disseminated intravascular coagulation after BT. HT was purer than BT. In vitro activities were similar.**

Conclusion: **Both BT and HT produced hypotension. HT appeared safer, because of higher purity. Regardless of source and purity, thrombin must be used with caution.**

Key Words: **Thrombin, Hypotension, Swine, Bovine, Human.**

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Thrombin is a serine protease (M_r 36,000) that plays the pivotal role in coagulation by converting fibrinogen to fibrin.[1] Although thrombin has numerous physiologic functions,[2] it is used medically for its ability to form fibrin. Thrombin is used alone for the control of bleeding from cannulation sites, for the treatment of aneurysms, and for ophthalmologic and burn surgery.[3–5] Thrombin is combined with cryoprecipitate or other fibrinogen sources to form liquid fibrin glues[6] that are used for a wide variety of surgical applications.[7] Thrombin has also been used as a component of dry fibrin sealants available commercially in Europe or under investigation in the United States.[8] The most widely used thrombin in the United States has been bovine thrombin. However, a new fibrin glue product that uses purified human thrombin has recently become available (Tisseel, Baxter Healthcare, Glendale, CA), and others are under investigation.[8]

Although thrombin is very useful clinically, important hemodynamic and immunologic problems have been identified. Fatal and near fatal hypotensive responses to fibrin glue have been reported.[9,10] These have been attributed to the accidental intravascular introduction of commercial bovine thrombin. The risk of accidental introduction of thrombin into the vasculature during procedures such as splenic or hepatic repair makes the hypotensive response to thrombin a major concern. This complication must be considered during any procedure in which thrombin or fibrin sealants are used on or near lacerated vascular structures.

The use of bovine thrombin has been associated with the development of immune coagulopathies. Patients exposed to bovine thrombin preparations have developed antibodies to thrombin; fibrinogen; and factors V, X, and XI.[11–14] Anaphylactic responses also have been reported.[15]

It is expected that the use of new, highly purified human thrombin preparations will reduce or eliminate the risks associated with development of antibodies to thrombin, or to impurities found in bovine thrombin preparations.[8] However, it is not known whether new formulations may be associated with hypotensive reactions. These potential responses are important to evaluate, as they may be a determinant in the overall acceptance of new fibrin sealant products. Thrombin has numerous vascular and hemodynamic effects that are receptor mediated.[16] In general, intravascular thrombin induces a reduction in peripheral vascular resistance while simultaneously inducing pulmonary hypertension and systemic hypotension. The precise response may vary depending on the species studied, the blood vessel studied, and the presence or absence of endothelium.[17] No study has been published that has compared the effects of intravascular bovine and human thrombin preparations. This information will be of importance, in light of the introduction of human thrombin for clinical use. Therefore, this study was conducted

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to characterize and compare the effects of intravascular injection of highly purified human thrombin and commercial bovine thrombin in swine. Additional objectives were to compare the activities of bovine and human thrombin on porcine fibrinogen and porcine platelets.

MATERIALS AND METHODS

Animals

Seventeen cross-bred commercial swine weighing 51.3 $\pm$ 4.1 kg (mean $\pm$ SEM) were used for the in vivo study. For the platelet aggregation study, six additional cross-bred commercial swine (46.0 $\pm$ 1.7 kg) were used. Animals were maintained in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International. Studies were approved by the Institutional Animal Care and Use Committees of William Beaumont Army Medical Center, El Paso, Texas, and the U.S. Army Institute of Surgical Research, San Antonio, Texas. Animals received humane care in accordance with the Guide for the Care and Use of Laboratory Animals.[18]

In Vivo Study

Animals were fasted 18 to 24 hours before the surgical procedure, with water allowed ad libitum. After premedication with glycopyrrolate and a combination of tiletamine HCl and zolazepam HCl (Telazol, Fort Dodge Laboratories, Fort Dodge, IA), anesthesia was induced with thiopental sodium. The swine were intubated, placed on a ventilator, and maintained with isoflurane. Carotid arterial and jugular venous catheters were placed surgically. A rectal temperature between 38.3° and 40.0°C and 15 minutes of stable mean arterial pressure (MAP) were required before further experimental procedures. Blood pressure and heart rate were recorded at 10-second intervals throughout the study period using a continuous data collection system (Micro-Med, Louisville, KY).

This study was developed on the basis of a 2 $\times$ 2 factorial design, with two thrombin types (bovine and human) and two thrombin doses (30 U/kg and 60 U/kg body weight). Animals were assigned randomly to receive one of the four treatments: 30 U bovine thrombin per kilogram body weight (Bov30), 60 U bovine thrombin per kilogram body weight (Bov60), 30 U human thrombin per kilogram body weight (Hum30), or 60 U human thrombin per kilogram body weight (Hum60). After three animals were assigned to each treatment group, additional animals were randomized to the Hum60 and Bov60 groups only. The numbers of animals in each of the groups were Bov30, n = 3; Bov60, n = 6; Hum30, n = 3; and Hum60, n = 5.

The bovine thrombin preparation used was Thrombostat (Parke-Davis, Morris Plaines, NJ). The human thrombin preparation was prepared by Baxter Healthcare. Each preparation was reconstituted to a concentration of 1,000 U/mL in sterile physiologic saline. Thrombin activity for each preparation was confirmed independently by Dr. Foster Irwin (GenTrac, Inc., Middleton, WI).

Treatments were infused via the jugular catheter over a 15-second period. The doses and rates of administration were selected to simulate the maximal accidental introduction of a bolus of thrombin during the use of fibrin glue for a procedure such as repair of a fractured liver or spleen. After treatment administration, animals were maintained under anesthesia and monitored for 30 minutes or until death, whichever came first. Death before 30 minutes was defined as a heart rate of zero. At 30 minutes, surviving animals were killed by an overdose of pentobarbital.

After completion of the study period, each animal was necropsied and examined grossly for evidence of intravascular coagulation. Brain, heart, skeletal muscle, lung, liver, spleen, and kidney samples were collected and examined histologically. The pathologist was blinded to treatment at the time of histologic evaluation.

Electrophoresis

Sodium dodecyl sulfate–acrylamide gel (7.5%) electrophoresis of the thrombin preparations was performed as previously described,[19] with approximately 100 μg protein run on each gel. Thrombin preparations (10–20 μg protein) were also analyzed using a capillary electrophoresis system (Model P/ACE 5510, Beckman Instruments, Chaska, MN) with a 50 cm $\times$ 50 μm (ID), weakly hydrophobic, dimethyl C4 phase-coated column (Supelco, Belafonte, PA). An analytical grade human thrombin was obtained from Sigma Chemical (St. Louis, MO) and used as a thrombin standard.

Analysis of In Vitro Thrombin Enzymatic Activity

Thrombin time was determined using an Electra 750 precision photo-optical plasma coagulation-timing instrument made by Medical Laboratory Automation (Pleasantville, NY). A fresh porcine fibrinogen solution (300 mg/mL) was made daily using a 0.154 mol/L sodium chloride solution (normal saline) at 37°C. High-purity (>95%) bovine and human thrombin (1,000 U/mL) solutions were prepared using a solution containing calcium chloride ($CaCl_2$)(0.050 mol/L) and albumin (70 mg/mL). Human calibration plasma, human fibrinogen control, and bovine thrombin control (Instrumentation Laboratory, Lexington, MA) were used as standards. All reagents were purchased from Sigma Chemical unless otherwise indicated.

The operation of the Electra 750, including calibration and controls, was performed as indicated by the operators' manual. This assay was derived from the standard thrombin time assay,[20] with the described modifications. The bovine and human thrombin solutions were prepared by serial dilutions using a $CaCl_2$ (0.05 mol/L) and albumin (70 mg/mL) solution, at room temperature. All reagents and materials were maintained at 37°C during the assay procedure. Thrombin test sample and porcine fibrinogen solution were combined and clot formation time was determined by standard methods. Final concentrations were 150 mg/dL porcine fi-

Table 1 Mean Arterial Pressure after Bovine or Human Thrombin (Mean ± SEM)

	Bov30	Bov60	Hum30	Hum60
Pretreatment MAP (mm Hg)	62 ± 4^{ab}	69 ± 2^{a}	52 ± 4^{b}	60 ± 3^{ab}
Initial nadir MAP (mm Hg)	16 ± 4	20 ± 3	24 ± 4	23 ± 3
Initial nadir MAP (percent of pretreatment MAP)	25.1 ± 5.8	29.3 ± 4.0	46.1 ± 5.7	38.1 ± 4.9
Time from treatment to MAP nadir (s)	83 ± 11	70 ± 8	77 ± 11	70 ± 10

^{ab} Different superscripts within row differ ($p < 0.05$).

brinogen, 35 mg/mL albumin, and 0.025 mol/L $CaCl_2$. All tests were performed in duplicate.

To confirm the activities of the two thrombins on a National Institutes of Health unit basis, prothrombin times for the bovine and human thrombins (2 U/mL) were performed with control human plasma, using standard procedures. Ten replicates of each thrombin type were analyzed. Prothrombin times for the bovine and human thrombins were 14.16 ± 0.18 seconds and 14.13 ± 0.13 seconds, respectively, and did not differ significantly.

Platelet Aggregation

The aggregation responses of porcine platelets to purified human thrombin, purified bovine thrombin, and the Parke-Davis bovine thrombin preparation were determined. Purified bovine and human thrombins were purchased from Sigma and reconstituted at 1,000 U/mL in a solution containing $CaCl_2$ (0.05 mol/L) and albumin (70 mg/mL). Thrombostat (Parke-Davis) was reconstituted in the same manner. Using an Electra 750 coagulation timing instrument, the thrombin preparations were adjusted to equal concentrations on the basis of thrombin activity units. Platelet aggregation assays were performed using a PACKS-4 aggregometer (Helena Laboratories, Beaumont, TX). Porcine blood was collected using sodium citrate as an anticoagulant. Blood was centrifuged at 550 × g for 10 minutes. Platelet-rich plasma was collected and washed two times with Hank's balanced saline solution. Platelets were counted and reconstituted at a concentration of 1×10^6/mL. Platelet aggregation studies were performed by standard methods at 37°C with a final thrombin concentration of 1 U/mL. The maximum aggregation was determined and expressed as percentage of full aggregation. One hundred percent aggregation was defined as the difference in light transmission through the platelet suspension and the Hank's balanced saline solution without platelets. Samples were analyzed in triplicate.

Data Analysis

All continuous data were analyzed by analysis of variance using the General Linear Model procedure of SAS (SAS Institute, Cary, NC).[21] Statistical models were used that accounted for the effects of thrombin type, thrombin dose, the thrombin type by thrombin dose interaction, and time. Preplanned comparisons were made by *t* test, with correction for multiple comparisons. Data are expressed as means ± SEM. Proportions of animals surviving the study period (60-U/kg groups only) were compared by Fisher's exact test using the FREQ procedure of SAS.[21]

RESULTS

In Vivo Study

All animals in the Bov30, Hum30, and Hum60 groups survived the 30-minute study period. Survival was greater ($p < 0.05$) in the Hum60 group than in the Bov60 group, in which one of six animals survived the study period. Mean survival time for animals that did not survive the study period was 326 ± 26 seconds.

An initial hypotensive response was observed after treatment administration in each group (Table 1). No differences among treatments were noted for either the time to nadir or the MAP at nadir of the initial hypotensive response. When data were expressed as percentage of pretreatment MAP and examined across doses, a main effect of thrombin type was detected. The MAP at the initial hypotensive nadir in pigs that received bovine thrombin was 27.7 ± 3.3% of the pretreatment MAP, which was lower ($p < 0.05$) than the mean of 41.1 ± 3.7% observed in pigs that received human thrombin.

Figure 1 depicts changes in the MAP with time relative to the initial MAP nadir, expressed as percentage of pretreatment MAP, for all animals. Within each treatment group, the MAP at nadir was significantly different from the pretreatment MAP ($p < 0.01$). In the Bov30 group, MAP returned to starting levels by 260 seconds after nadir. The Hum30 group returned to pretreatment MAP by 50 seconds and the Hum60 group returned by 120 seconds. The Bov60 MAP did not return to pretreatment MAP at any time. The MAP for the four groups followed similar patterns through 30 seconds after nadir. At 40 seconds, MAP in the Hum30 and Hum60 groups were higher ($p < 0.05$) than in the Bov30 and Bov60 groups, which did not differ. MAP in the Bov30 did not differ significantly from the Hum30 or Hum60 groups after 230 seconds after treatment. In the single Bov60 animal that survived the study period, MAP returned to levels similar to the starting MAP.

In all treatment groups, vascular congestion and atelectasis were observed to some degree. Intravascular thrombi, ranging from diffuse microscopic thrombi to grossly apparent clots within the vena cava, heart chambers, pulmonary artery, and aorta, were observed only within the Bov60 group. Evidence of disseminated intravascular coagulation (DIC) was much more extensive in the Bov60 group than in the Hum60

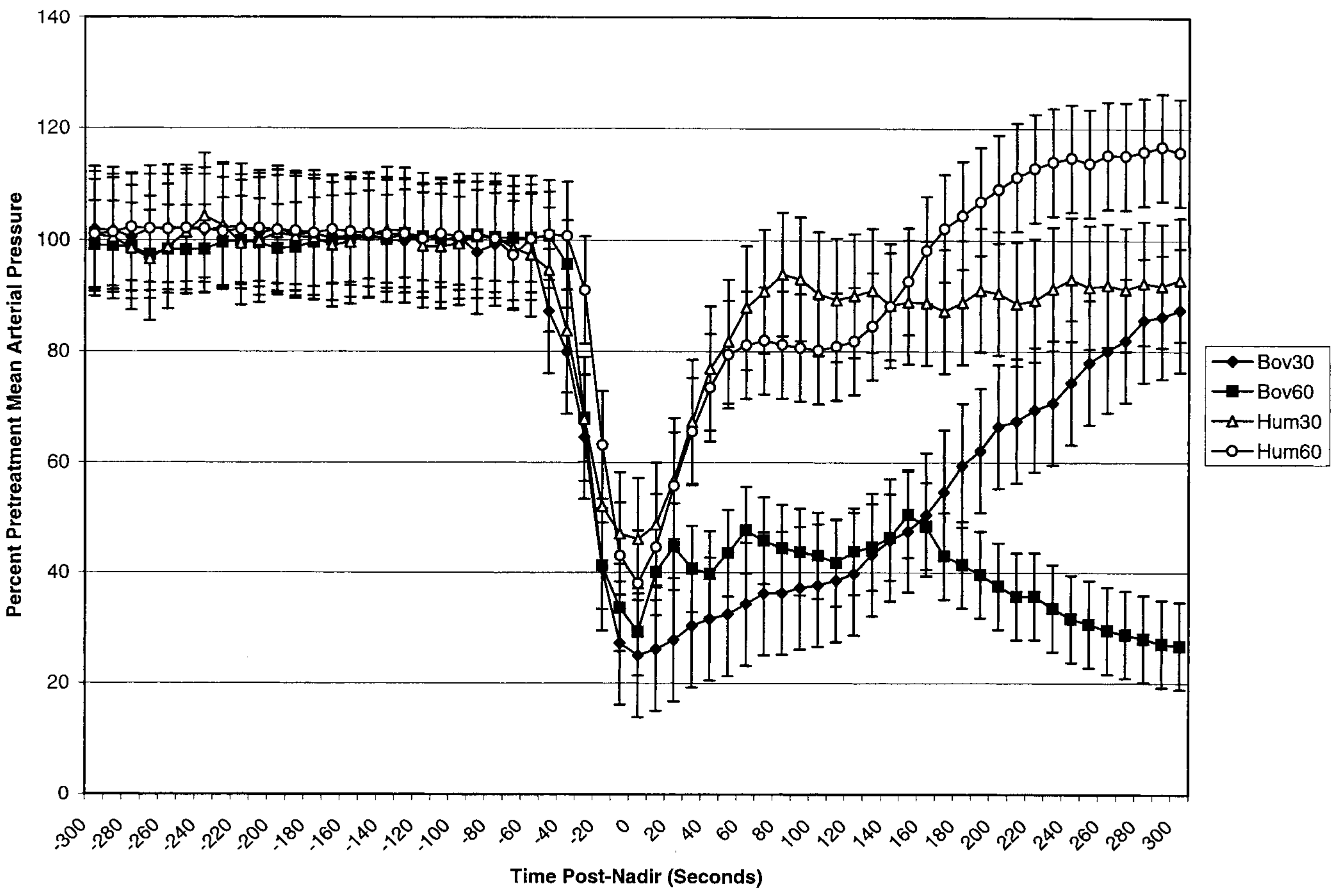

Fig. 1. *Initial hypotensive response and postnadir recovery in swine infused with various thrombin preparations. All animals are included (Bov30, n = 3; Bov60, n = 6; Hum30, n = 3; Hum60, n = 5). Time 0 is the nadir of the initial hypotensive response. Means and SEM are shown.*

group. At the 30-U/kg body weight dose, evidence of DIC was greatly reduced for both thrombin types. Consistent with the results at the 60-U/kg treatments, gross and histologic evidence of DIC was more extensive in the Bov30 than in the Hum30 group.

Electrophoresis

Gel analysis of the Parke-Davis bovine thrombin preparation (Fig. 2*B*) indicated several protein bands of various sizes, including a thrombin band at M_r 36,000, similar to that of the thrombin standard (Fig. 2*C*). In contrast, the Baxter Healthcare human thrombin preparation yielded a prominent albumin band (M_r 66,000) with a faint band of thrombin (Fig. 2*A*). It was reported by the suppliers that the albumin was added to the human thrombin preparation as a stabilizer. Capillary electrophoresis of the bovine thrombin preparation resulted in several peaks including that of thrombin (Fig. 3*B*). Analysis of the human thrombin preparation revealed a major peak (presumably albumin) with two other minor peaks, one of which was thrombin (Fig. 3*A*). The location of thrombin is shown clearly in the profile for the thrombin standard (Fig. 3*C*, *arrow*). Data indicate that the human thrombin preparation from Baxter Healthcare was much more pure than the Parke-Davis bovine thrombin preparation. In the Parke-Davis bovine thrombin preparation, 25% of the protein present was thrombin. In the Baxter Healthcare human thrombin, 6% of the protein was thrombin.

Analysis of In Vitro Thrombin Activity

For both bovine and human thrombin, the relationship between thrombin concentration and clot formation time was logarithmic for thrombin concentrations between 0.78 and 12.5 U/mL (Fig. 4). The relationship is described by the equation time = −2.17 (natural log thrombin concentration) + 14.06 ($R^2 = 0.96$), for bovine thrombin. For human thrombin, the relationship is described by the equation time = −2.90 (natural log thrombin concentration) + 14.16 ($R^2 = 0.92$). Clot formation times did not differ between bovine and human thrombin at any concentration studied.

Platelet Aggregometry

There was no effect of thrombin type on aggregation of porcine platelets. Platelet aggregation was 31.7 ± 4.1%, 29.5 ± 4.1%, and 32.4 ± 4.1%, in response to 1 U/mL purified bovine thrombin, Parke-Davis bovine thrombin, and purified human thrombin, respectively.

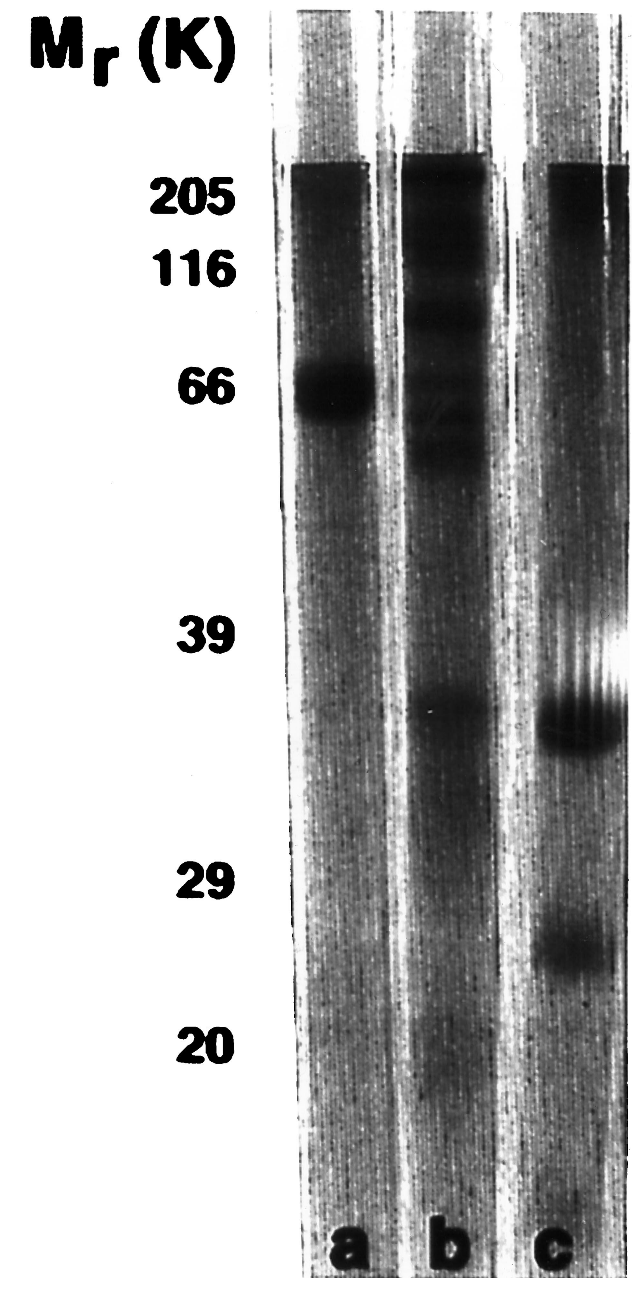

Fig. 2. *Sodium dodecyl sulfate–acrylamide gel electrophoresis of bovine and human thrombin preparations. (*a*) Human thrombin preparation (Baxter Healthcare), (*b*) bovine thrombin preparation (Parke-Davis), and (*c*) human thrombin standard (Sigma Chemical). Thrombin band is located at* M_r *36,000.*

DISCUSSION

The purities of the thrombin preparations used in this study were markedly different, with the human preparation more pure than the bovine. It is clear from Figures 2 and 3 that thrombin constitutes only a fraction of the total material contained in each of the preparations. The presence of impurities in bovine thrombin preparations has been previously demonstrated.[22,23] Immunologic data from patients suggest that the Parke-Davis bovine thrombin formulation contains factors V, X, and XI.[11–14] Kallikrein has also been identified in this bovine thrombin product (D. Frazier, personal communication).

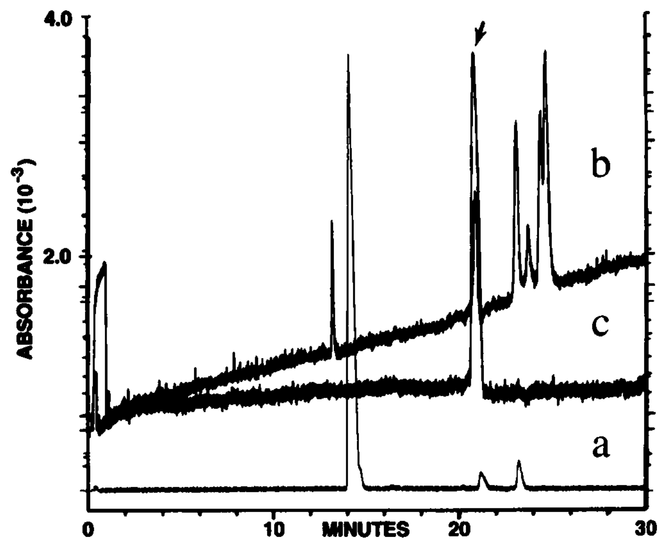

Fig. 3. *Capillary electrophoresis of bovine and human thrombin preparations. (*a*) Human thrombin preparation (Baxter Healthcare), (*b*) bovine thrombin preparation (Parke-Davis), and (*c*) human thrombin standard (Sigma Chemical).* Arrow *indicates thrombin.*

In the current study, DIC occurred after intravenous infusion of either bovine or human thrombin, as indicated by the findings of grossly visible intravascular clots, intravascular microthrombi, and vascular congestion. At the 60-U/kg body weight dose, the DIC induced by bovine thrombin was much more severe than that induced by human thrombin. In the Bov60 group, just 17% of the pigs survived the 30-minute study period, compared with a 100% survival rate in the Hum60 animals. At the 30-U/kg body weight dose, gross and histologic evidence of DIC were also more extensive in the bovine thrombin group than in the human thrombin group. Similar dosages have been used previously to produce DIC.[24–26] No previous study has compared the DIC responses to thrombin preparations from two different species, or with two markedly different purities.

Thrombin enzymatically converts fibrinogen to fibrin. The structures of bovine and human thrombin are different, although there is a high degree of conservation in the regions that constitute the enzymatically active site.[1] There are also species differences in the structure of fibrinogen.[27] The thrombin doses used in this study were standardized on the basis of the National Institutes of Health unit, which is a measure of thrombin activity with human fibrinogen as a substrate. Conceivably, the two thrombins could have differing activities on porcine fibrinogen. A difference of this nature could explain a difference in DIC. To address this possibility, we examined the rates at which bovine and human thrombin convert porcine fibrinogen to a detectable clot. The enzymatic activities of the two thrombins were similar

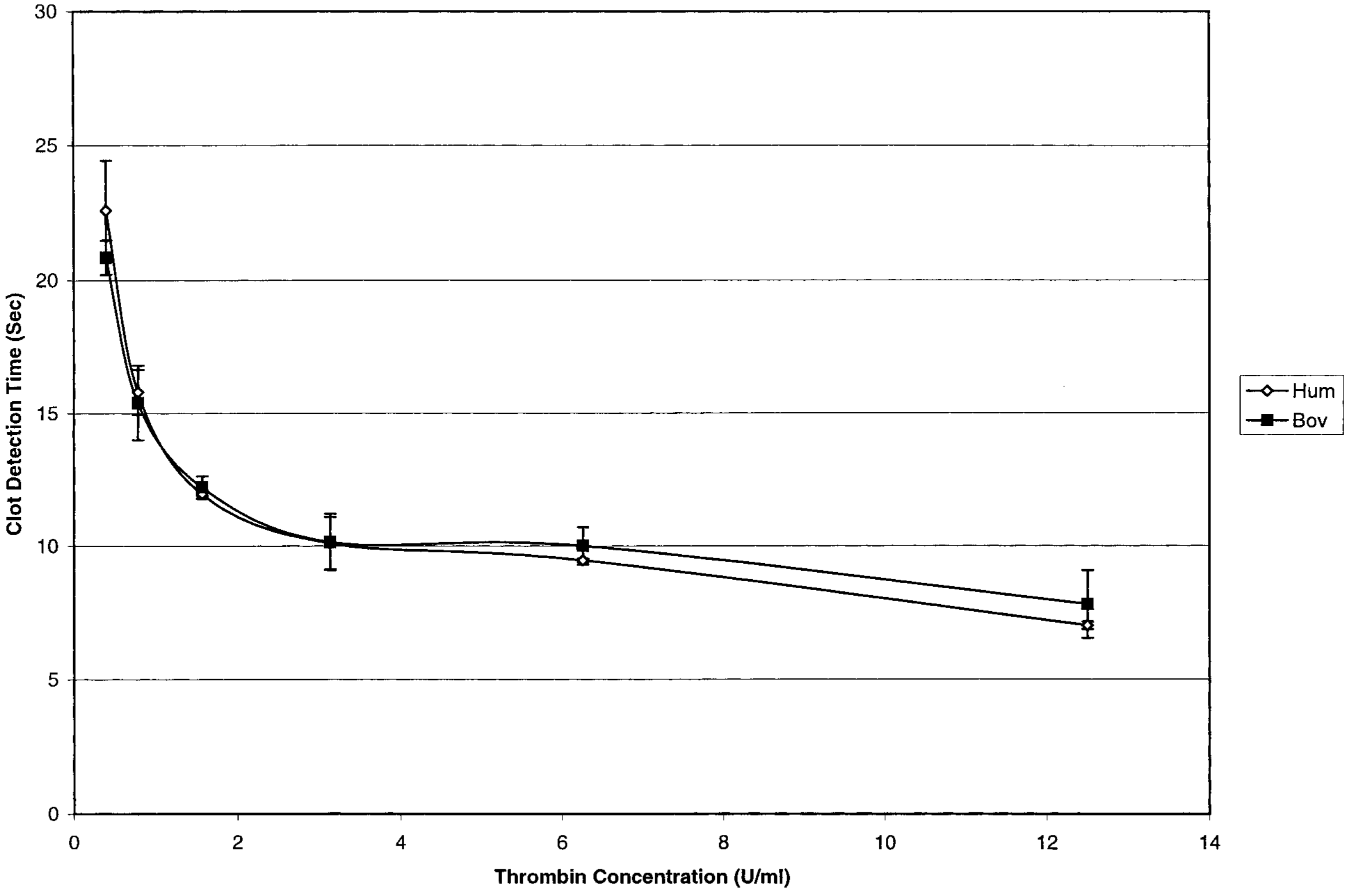

Fig. 4. *Activities of bovine and human thrombin with porcine fibrinogen as a substrate. Mean clot formation times and SEM are shown. Data represent 10 replicates of each thrombin type at each concentration.*

(Fig. 4). Therefore, the differences in the degree of DIC cannot be explained by differences in thrombin enzymatic activity.

Activation of platelets by thrombin is mediated by specific receptors on the platelet membrane, and is dependent on the enzymatic activity of the thrombin molecule.[2,16] A higher degree of platelet activation could result in more extensive DIC. Species differences in the responsiveness of platelets to thrombin are known.[28] However, a difference in the responsiveness of platelets on the basis of the species from which the thrombin was derived has not been confirmed. In one study, bovine thrombin had a slightly higher affinity for human platelets than did human thrombin, but in terms of platelet activation, the authors concluded that the two thrombins were nearly functionally identical.[29] In other studies in which bovine and human thrombin have been compared in their abilities to effect receptor-mediated events, the results have been similar for the two thrombins,[30–32] although differences were detected in one study.[33]

In the current study, the aggregation of porcine platelets was similar in response to bovine and human thrombin. The aggregation responses of porcine platelets to the thrombins, which ranged from 29.5% to 32.4%, are consistent with previous reports of responses between 13% and 52%.[34,35] Differences among species in the platelet aggregatory response to thrombin have been documented.[35] This is the first reported comparison of the responses of porcine platelets to thrombins from different species. The platelet responses to bovine and human thrombin did not differ, suggesting that differences in platelet activation by the injected thrombin treatments cannot explain the differences in DIC noted. The finding that the aggregation response to the Parke-Davis thrombin preparation was similar to the observed responses to the purified bovine and human thrombins suggests that impurities present in the Parke-Davis preparation do not directly activate platelets.

Another possible explanation for the differing degrees of DIC observed is that the infusion of the bovine preparation may have resulted in an accelerated conversion of native prothrombin to native thrombin. As mentioned earlier, the Parke-Davis topical bovine thrombin preparation appears to contain factors V, X, and XI. Because thrombin directly activates factors V and XI,[36] it is possible that these coagulation factors are converted to the active form once the preparation is reconstituted. Both the activated and proenzyme forms of factor X have been isolated from this product.[22]

Activated factors V, X, and XI, as well as thrombin, contribute directly or indirectly to formation of the prothrombinase complex.[2,37] Therefore, the presence of factors V, X, and XI in the bovine thrombin preparation may lead to an increased rate of assembly of the prothrombinase complex, with a resultant increase in intravascular conversion of native prothrombin to thrombin. Additionally, the presence of kallikrein in the preparation may contribute to the activation of the intrinsic clotting cascade and thereby lead to the generation of native thrombin.[38] The generation of thrombin by bovine thrombin preparations has previously been documented in vitro.[22] Increased generation of native thrombin from native prothrombin through the actions of impurities present in the Parke-Davis bovine thrombin is the most likely explanation for the differences in DIC noted between bovine and human thrombin.

Thrombin dosages as low as 4 to 10 U/kg body weight have elicited transient hypotension experimentally.[33,39] The vascular response to thrombin is receptor mediated[2,16] and varies, depending on the functional status of the endothelium, the blood vessel involved, and the species studied.[17] In general, when thrombin acts on the endothelium, there is an endothelium-dependent vasodilation that is mediated by nitric oxide. When thrombin acts directly on vascular smooth muscle, vasoconstriction results.[17] The transient hypotensive response to thrombin is believed to be primarily attributable to peripheral vasodilation, with subsequent reduction in peripheral vascular resistance.

For each of the thrombin types and doses studied, there was an initial, rapid decline in MAP (Fig. 1) and the initial patterns of decline were similar. During the postnadir recovery from the initial hypotensive response, the patterns in the bovine and human thrombin groups differed. The hypotensive response was more profound and prolonged in the Bov30 and Bov60 groups. Five of six animals in the Bov60 group failed to return to starting MAP and died. In the Bov30 group, the MAP returned to the preinfusion level by 240 seconds after nadir, whereas the Hum30 and Hum60 groups returned by 50 and 120 seconds, respectively. Between 40 and 240 seconds after nadir, MAP was lower in the Bov30 than in the Hum30 or Hum60 groups (Fig. 1).

It is possible that the prolonged hypotensive response observed in the pigs that received the bovine thrombin preparation was the result of a greater potency of bovine thrombin in activating porcine vascular thrombin receptors. Both human and canine thrombin were more potent than bovine thrombin in decreasing vascular resistance in a canine hindlimb perfusion model.[33] However, when bovine and human thrombins were compared using canine vessels in vitro, similar responses were demonstrated.[30,31] In another study, infusion of bovine or human thrombin into the basal ganglia of rats produced similar edema for the two thrombin types.[32] The ability of thrombin to activate thrombin receptors is dependent on the enzymatic activity of thrombin. The similar enzymatic activities of bovine and human thrombin reported here suggest that a difference in the ability of the two thrombins to activate thrombin receptors would not be expected. Additionally, we have shown that human and bovine thrombins yield similar aggregation responses in porcine platelets. Taken together, currently available data suggest that a difference in the abilities of bovine and human thrombin to activate porcine vascular thrombin receptors is not likely.

As discussed earlier, the bovine thrombin preparation may have caused an increase in the conversion of native prothrombin to native thrombin, attributable to impurities. This phenomenon could explain the deeper and more prolonged hypotensive response observed with the bovine thrombin preparation. Another explanation may be that one or more of the impurities were vasoactive. Factor Xa is a vasodilator that may act through a receptor similar to the two known thrombin receptors.[40] The presence of kallikrein in the bovine preparation raises the possibility of the generation of bradykinin, a potent vasodilator.[38]

Thrombin purity appears to be very important. The presence of impurities in the bovine thrombin preparation is the most likely explanation for the differences in the DIC and hypotensive responses observed in this study. The physical form of the thrombin used may also be important. Hypotensive responses after the use of thrombin as a component of fibrin glue have been reported.[9,10] However, this has not been reported after the use of thrombin in the form of a dry fibrin sealant. In studies in which thrombin has been used experimentally as a component of dry fibrin sealants in dogs,[41] goats,[42] rats,[43] and swine,[44] no hypotensive responses related to the hemostatic bandages have been reported. Additionally, there have been no published reports of hypotension after the use of thrombin as a component of dry fibrin sealants available for human use in Europe.

Our findings suggest that the purity of the thrombin preparation chosen for surgical use is extremely important. The purities of commercial thrombin preparations may vary greatly. Purity should be known before use. Although it appears that the purified human preparation is safer than the bovine preparation, a profound hypotensive response to intravenous human thrombin was demonstrated in this study. Caution must be exercised in the clinical use of thrombin preparations, regardless of source and purity.

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